REMARKS

Claims 23-42 are pending in this application.

I. The Invention

The invention is an injectable material for soft tissue augmentation, methods of preparing an injectable material for soft tissue augmentation, and also includes methods of soft tissue augmentation in which the injectable material is used. The injectable material can be used to aesthetically correct scars, wrinkles, and other similarly depressed dermal defects by filling the depression that creates the defect.

The injectable material includes blood plasma proteins, such as serum albumin proteins, very low density lipoproteins, low density lipoproteins, high density lipoproteins, immunoglobulins, fibrinogen (the precursor to FIBRIN), prothrombin, transferring, and other transport proteins. The blood proteins used in the injectable material form a material that has sufficient mass or body such that it acts as a filler of the depressed defect. The proteins contain cross-links between and among each of the individual molecules. The cross-linkages include at least one intermolecular amide bond.

The injectable materials and the methods of the invention meet a need in the art for a safe, non-antigenic, non-irritating, aesthetically pleasing soft tissue augmentation material that is longer lasting (*i.e.*, fills a depressed defect for a longer period of time) than the prior art materials. The injectable materials of the invention are easily injected, and once injected are more resistant to degradation by the natural proteases that are present in the intradermal compartments of human skin. These properties are advantageous, particularly as the environment in which a tissue augmentation device is used (dermal compartments of human skin) is populated by both proteases and components of the immune system that function to degrade most types of conventional tissue augmentation devices, or are provoked into initiating an irritating and potentially harmful humoral or non-humoral response.

II. The Rejection of Claims 23-42 under 35 U.S.C. § 103(a).

The Examiner has rejected claims 23-42 under 35 U.S.C. § 103(a), asserting such claims are unpatentble over the disclosure of Coleman or Pollack taken in view of:

1. Grabarek et al., Analytical Biochemistry, Vol. 185, pp. 131-135 (1990) ("Grabarek"); or

2. Wong, Chemistry of Protein Conjugation and Cross-linking, pp. 39-40 and 195-207 (1991) ("Wong"); or

3. Wang, et al., Journal of the Parenteral Drug Assoc., Vol. 34, No. 6, pp. 452-462 (Nov.-Dec. 1980) ("Wang").

The Examiner contends that both Coleman and Pollack show the administration of an injectable material in combination an anesthetic compound such as lidocane into an intradermal compartment of the skin of the patient as well as a method of preparing the composition. However, the Examiner concedes that neither teaches the use of cross-linked blood plasma proteins wherein the linkages comprise at least one intermolecular amide bond.

The Examiner asserts that Grabarek teaches use of cross-linking agents for the purpose of cross-linking protein-protein complexes, including use of zero-length-cross-linking procedures. Wong, according to the Examiner, teaches various zero-cross-linking reagents for the purpose of creating stable bonds between two intrinsic chemical moieties or one of one or more polypeptide chains. Finally, the Examiner contends that Wang teaches numerous physiologically acceptable fluids as additives for parenteral formulations, including anesthetic compounds. None teaches, discusses, or suggests the use of the disclosed processes or reagents to produce and injectable material for tissue augmentation comprising intermolecular cross-linked blood plasma proteins wherein the cross-linkages comprise at least one amide bond.

The Examiner sums up his argument by stating:

> Thus, in view of the above, and in view of the combined teachings of the prior art; [sic] one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known injectable material for soft tissue augmentation comprising cross-linked, blood plasma proteins which are cross-linked, wherein the cross-linkages comprise at least one intermolecular amide bond with a zero-length-cross-linking agent... .

Office Action at pages 6-7 (emphasis added).

In the Office Action, the Examiner states that he does not consider the applicants' previous arguments to be persuasive because, he asserts, Coleman and Pollack "clearly disclose" an injectable material for soft tissue augmentation of wrinkles comprising cross-linked blood

plasma proteins. However, other than this bald statement, the Examiner has made no showing nor has he provided an explanation as to where the disclosure of cross-linked blood plasma proteins occurs in Pollack or Coleman.

III. The References Relied Upon by the Examiner.

A. Coleman

Coleman teaches a composition for treating wrinkles and scars that contains a mixture of porcine gelatin powder (collagen), sterile saline, and ε-amino caproic acid. This mixture is sold under the tradename "FIBREL." When administered, Coleman teaches that FIBREL may mixed with a patient's plasma prior to injection. Coleman teaches that FIBREL was designed to stimulate collagen production by the patient's own cells at the site of injection. Col. 1:22-23. Coleman also discloses that use of the composition without the addition of the patient's blood plasma is as effective as use of the composition that does contain the blood plasma. In fact, Coleman advises that use of FIBREL without the blood plasma is additionally advantageous as it avoids any chance of inadvertent contamination of the physician or the physician's assistant with the blood plasma mixture during mixing. Col. 1:37-41. Coleman does not teach or suggest that the blood plasma that may be used to reconstitute the FIBREL powder contains blood plasma protein that have any cross-linkages at all, let alone cross-linkages comprising at least one amide bond.

B. Pollack

Similarly, the Pollack reference teaches use of FIBREL for the treatment of scars or wrinkles. Pollack teaches that the FIBREL product is "individually reconstituted for each patient treatment session." To accomplish this, a small amount of the patient's plasma is added to a FIBREL, a mixture of highly purified, denatured porcine collagen (gelatin) and ε-amino caproic acid. Pollack teaches that once injected, the gelatin of the FIBREL composition acts as a temporary matrix upon which the blood plasma constituents, such as fibrin, are deposited Pollack teaches that the ε-amino caproic acid is present in FIBREL to inhibit the "digestion of fibrin, by inhibiting the production of fibrolysin." Pollack teaches that FIBREL acts by activating the patient's own fibroblasts, thereby inducing subsequent collagen deposition by those cells. Pollack does not teach or suggest that any of the components of the blood plasma added into the FIBREL composition are cross-linked, or even associated with one another in any

manner. Nor does Pollack suggest that the cross-linking of the blood plasma proteins incidentally present in the blood plasma used to reconstitute the FIBREL is either desirable or necessary. Pollack makes clear that it is not the blood plasma proteins that are acting to augment the targeted tissue area, but rather that it is the subsequently deposited collagen, which is secreted by the patient's own cells.

C. Grabarek, Wang, and Wong

Grabarek teaches a two-step procedure for zero-length cross-linking using active esters. Similarly, Wong teaches various zero-cross-linking reagents for the purpose of creating stable bonds between two intrinsic chemical moieties or one of one or more polypeptide chains. Wang teaches physiologically acceptable fluids and additives for parenteral formulations.

IV. The Combination of Coleman or Pollack with Grabarek, Wang, and Wong Do Not Render Obvious the Claimed Invention.

To establish a *prima facie* case of obviousness based upon a combination of references, the Examiner must show: (1) that the combination of references teaches or suggests all elements of the invention as claimed; (2) that there is in the art a motivation or suggestion to make such combination; and (3) that a person of ordinary skill in the art would have a reasonable expectation that such combination would be successful.

In the present case, the Examiner has failed to satisfy all of the above requirements for a *prima facie* case of obviousness. First, there is simply no teaching of cross-linked blood plasma proteins of any kind in Pollack or Coleman. The Examiner, while insisting the contrary, has provided no explanation or basis for the assertion, nor has he cited to any specific portion of Coleman or Pollack that lends support to this proposition; none of the references teaches cross-linked blood plasma proteins. Coleman and Pollack merely disclose the use of FIBREL, which uses the connective tissue protein collagen to fill depressed defects. As disclosed in each of Coleman and Pollack, the FIBREL composition is made of porcine gelatin (a collagen) and ε-amino caproic acid. The FIBREL composition itself does not constitute any blood plasma proteins. As known to one of skill in the art, a collagen is not a blood plasma protein, but is rather any of a group of fibrous proteins that form the main component of connective tissue in mammals. *See* specification at page 8; Declaration of Rozlyn Krajcik under 37 C.F.R. § 1.132

(hereinafter "Dec.") at ¶ 26, submitted with the Amendment filed June 19, 2003. ε-amino caproic acid is not a protein at all.

Notably absent from both Coleman and Pollack is any suggestion that the collagen in the FIBREL is cross-linked. Indeed, the Pollack reference expressly teaches that the "mode of action" of FIBREL involves the activation of the patient's own fibroblasts and subsequent collagen deposition by those cells, *i.e.*, deposition of host collagen, which production and/or deposition at the target augmentation site is induced by the FIBREL injection. Pollack at col. 1, ll. 28-32. *See* also, Coleman at col. 1, lines 22 and 23.

Moreover, there is not teaching in wither Coleman or Pollack that any proteins that may be present in the blood plasma used to reconstitute the FIBREL composition are cross-linked in any manner. There is no factual or technical basis that would have caused a person of skill to believe that the blood plasma used in the reconstitution step described in Pollack or Coleman inherently discloses plasma having amide cross-linked blood plasma proteins. Neither reference discusses or even alludes to any process by which such cross-links would be formed in the collected blood plasma. Dec. at ¶ 26. Neither Coleman nor Pollack teaches that the blood plasma to be used for reconstitution of FIBREL is treated in any way so as to induce, encourage, or facilitate the formation of cross-linkages that include amide bonds. The references merely state that the blood plasma is mixed with the FIBREL powder to reconstitute it, and even that use of blood plasma itself is unnecessary. Dec. at ¶ 25.

Applicants have submitted the Physician Package Insert that accompanies the FIBREL product for the Examiner's review. Dec. at ¶ 20. The Package Insert serves as confirmation that the blood plasma used in the reconstitution of FIBREL as taught in Coleman and Pollack is not treated or otherwise subjected to any processes that would result in the formation of amide bond cross-linkages of any constituent blood plasma proteins, or any other type of cross-linkages. Dec. at ¶ 27. In fact, one of skill would understand that any formation of linkages in the blood plasma is discouraged. The Package Insert discloses that the anti-coagulant citrate dextrose is added to the blood sample to prevent blood coagulation. Dec. at ¶ 27. Anti-coagulants are known in the art to prevent the cascade of enzyme mediated reactions that result in clotting, *i.e.*, the formation of bonds between various blood proteins. Thus, Pollack and Coleman discloses that the formation of cross-linkages between and among blood plasma proteins is undesirable. Dec. at ¶ 27.

Furthermore, a person of skill in the art upon reading Coleman and Pollack, would understand that there are no amide bonds formed between the blood plasma proteins present in the patient's plasma, as the formation of such bonds does not occur spontaneously and casually in nature. Dec. at ¶ 27-29. This is also illustrated by the examples presented in the patent application itself. Dec. at ¶ 31-36. Attempts at tissue augmentation using blood plasma alone, as seen in Comparative Use Example 1, were unsuccessful, in comparison to tissue augmentation carried out using the composition of the invention. *See*, Table 1, comparing Comparative Use Example 1 to Use Example 1; Dec. at ¶ 33-35.

The addition of Grabarek, Wong and/or Wang does not remedy this deficiency. Grabarek does not teach or suggest compositions for use in tissue augmentation,. Additionally, the proteins upon which the two step zero-length cross-linking procedure are practiced are obtained from rabbit back and leg muscles, and <u>are not blood plasma proteins</u>. In Wong, only a general disclosure of zero-length cross-linking procedures is provided, and Wang teaches only use of suitable vehicles and additives for injectable compositions.

Additionally, even if each element of the invention was taught by the combination, which they are not, a person of skill in the art would not have been motivated to make the combination proposed by the Examiner. Both Coleman and Pollack teach use of FIBREL for tissue augmentation. FIBREL, as the references themselves disclose, acts to fill by recruiting fibroblasts which then secrete collagen, which itself then acts as the substance that results in augmentation. No proteins, blood plasma proteins or otherwise, are involved in the augmentation aspect of the composition. This is the reason that, as taught in Pollack, FIBREL is just as effective when used without reconstitution in the patient's plasma. Thus, a person of skill in the art would not have been motivated to take blood plasma proteins, a completely different type of filler from that taught in Coleman and Pollack, and, proteins that are ordinarily soluble and biodegradable within the body, and cross-link them in order to arrive at the present invention.

Finally, a person of skill in the art would not have had a reasonable expectation of success in making the combination of these references, as stated above, Coleman and Pollack teach use of collagen as a filler substance, collagen that is secreted by the patient's own cells. A person of skill in the art would understand that blood plasma proteins, which are normally soluble and biodegradable and do not serve any cell signaling or recruiting function, are not

capable of recruiting fibroblasts to enable the secretion of collagen, and the subsequent "filling" of the intradermal skin compartment into which the composition is injected. Thus, a person of skill in the art reviewing Coleman/Pollack and the secondary references, would have had no reasonable expectation that combination of such references would result in a tissue augmentation device that comprises blood proteins which are cross-linked, wherein the cross-linkages include at least one amide bond. The Examiner's comments to this point are unclear as stated in Paper 22. However, it is merely meant that because blood plasma proteins and collagen do not carry out a filling function by the same mechanism, a person of skill would hardly have been motivated to "switch-out" the collagen of FIBREL for blood plasma proteins.

Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the § 103(a) rejection.

V. The Non-Obviousness of the Claims is Supported By Secondary Considerations.

For the reasons, discussed above, the Examiner has failed to demonstrate *prima facie* obviousness. However, even if such case had been made, it is rebutted by the unexpected result achieved by the invention.

Namely, the tissue augmentation composition of the invention, once injected, last longer than the prior art compositions that use collagen as does FIBREL, for the inventive composition it is less rapidly degraded by the proteases and immune system components present in the human patient. Supporting data can be seen at least in the specification at, *e.g.,* Table 1 and Figure 1.

Table 1 compares the longevity of the filler masses produces by the composition of the invention (Use Example 1) and the collagen-containing prior art compositions (Comparative Example Uses 3 and 4). As is shown in Figure 2, when evaluated *in vivo*, the fillers of Comparative Uses 3 and 4 were almost completely degraded (average rating of 0.30) by day 526.

In contrast, the tissue augmentation composition of the invention was found to have an average rating of 3.019 by day 693. This demonstrates that the ability to withstand degradation and thereby function as a longer lasting augmentation device is substantially increased by the invention composition, in comparison to prior art collagen containing devices. Such results are unexpected, as both uncrosslinked plasma proteins (Comparative Use 2) and cross-linked collagen (Comparative Use Example 3; ZYPLAST) exhibit relatively rapid degradation.

CONCLUSION

It is respectfully submitted that the claims are not obvious over the cited prior art. Accordingly, it is requested that the Examiner consider and allow claims 23-42 at the earliest opportunity, and issue a Notice of Allowance.

Should the Examiner wish to discuss the claims, the art, or any of the issues addressed or raised in this response, he is requested to contact the undersigned at the telephone number given below.

Respectfully submitted,

Norman Orentreich, *et al.*

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By: Kristyne A. Bullock

KRISTYNE A. BULLOCK
Registration No. 42,371
AKIN GUMP STRAUSS HAUER & FELD LLP
One Commerce Square
2005 Market Street, Suite 2200
Philadelphia, PA 19103-7013
Telephone: 215-965-1200
Direct Dial: 215-965-1348
Facsimile: 215-965-1210
E-Mail: kbullock@akingump.com

KAB:cmb

5236238